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GANGLIONIC BLOCKING AGENTS

With Special Reference to the Effect of Hexamethonium on the Cardiovascular System

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1. The Principles of Ganglionic Blockade

Drugs which paralyze transmission in autonomic ganglia fall into two groups. In the first are drugs like nicotine which depolarize the ganglion cells, so that before they paralyze transmission they actually stimulate the ganglion more or less vigorously. Although the foundations of our knowledge of the autonomic nervous system rest on work done with nicotine, this is not suitable for use clinically, partly because of this initial excitant action, partly because it can, in addition, excite the chemoreceptors of the carotid bodies, cause neuromuscular block and produce certain central stimulant effects. The clinically useful ganglion blocking drugs belong to the second category and include such agents as tetraethylammonium ($N^+(C_2H_5)_4$) and hexamethonium ($N^+CH_3)_3.(CH_2)_6N^+(CH_3)_3$). These substances have a purely inhibitory effect on transmission through a ganglion. They act in a way which is usually termed competitive: that is, they compete with the acetylcholine released at the preganglionic nerve terminals for the specific receptors on the ganglion cell bodies. Their action is thus comparable to that of other competitive blocking agents, such as curare at the neuromuscular junction, atropine at a peripheral parasympathetic site, or mepyramine in antagonizing the effects of histamine. It is unfortunate that only rarely have the quantitative investigations necessary to prove such competition been made. But the general belief that these drugs act in this way agrees with all their known properties and provides a satisfactory working hypothesis of their mode of action. (For further details of the pharmacology of such drugs, see Paton, 1951; Paton & Perry, 1951a, 1951b; Paton & Zaimis, 1948, 1949, 1951 and Paton & Zaimis, 1952; Wien & Mason, 1951.)

a. Distribution of Hexamethonium in the Body

Hexamethonium owes its ability to compete with acetylcholine to the fact that, like acetylcholine, it is a compound of quaternary nitrogen; almost all the other agents with similar actions are also quaternary salts. This fact is responsible for many of the characteristics of ganglion blocking agents. Drugs penetrate cell membranes much more rapidly in the unionized form than as ions; consequently quaternary salts, which in solution can exist only in the ionized form, penetrate the cellular structures of the body very slowly, and in fact have a predominantly extracellular distribution. To this may be attributed: (i) the slowness of absorption of hexamethonium from the intestine (Milne & Oleesky, 1951; Harington, unpublished); (ii) the slowness of penetration of hexamethonium into the cerebrospinal fluid (Paton, unpublished); (iii) the distribution of hexamethonium in the extracellular fluid of the body (Morrison & Paton, unpublished); (iv) the excretion of hexamethonium, like inulin, without tubular reabsorption or secretion (Young, de Wardener & Miles, 1951).

The slowness of absorption from the intestine makes oral administration difficult in clinical practice, not so much because the absorption is usually only about 5–10% of the dose given, but because the percentage of absorption is variable; it may be as little as 2% and yet occasionally as high as 30%. Harington (unpublished) has shown that absorption depends to some extent on the salt of hexamethonium used, the bromide being appreciably better absorbed than the chloride, tartrate, or methosulphate. He has also shown that absorption is greater as well as somewhat slower when hexamethonium is taken on an empty stomach. Many of the difficulties of oral administration could be overcome if the absorption could be made regular even if it were not at the same time increased.

b. Antagonists

The interruption of autonomic activity at the ganglionic level by ganglion blocking drugs has the advantage that their effects can be antagonized when necessary by sympathomimetic or parasympathomimetic substances which act peripherally. Because of the fairly ready excretion of hexamethonium, antidotes to its effects are not often needed, particularly as experience is gained in using the drug. If such antidotes are necessary, noradrenaline or sympathomimetic amines may be used when too great a fall in blood pressure has been produced; or carbachol, urecholine or neostigmine may be used if intestinal stasis or ileus has developed.

The use of drugs which actually antagonize hexamethonium at the ganglion itself is still poorly understood. In general, anticholinesterases (the logical antidotes) have a much less dramatic action at the ganglionic synapse than at the neuromuscular junction. Some successful antagonisms to the actions of ganglionic blocking agents by anticholinesterases have been described, but special conditions are usually necessary for this and a casual test for such action usually fails to reveal it. In man, Grob & Harvey (1950) have found that prostigmine could not prevent the postural hypotension caused by pentamethonium, and this result is entirely concordant with general experience with animals.

c. Selectivity

Although ganglion blocking agents will paralyze all ganglia if given in sufficient dose, ganglia usually differ somewhat in their sensitivity. Thus, in the cat, the ganglia of the salivary gland seem particularly sensitive to most agents, whereas part of the superior cervical ganglion is very resistant to blockade. Similar differences occur in man, and subjects vary considerably in the relative proportion of ocular, hypotensive and intestinal effects produced by a given dose of hexamethonium. Because different drugs varied in the incidence of their action in animals, it was hoped that blocking agents fairly specific to particular ganglia in man could be found, but specificity of this sort great enough for clinical usefulness has not yet emerged.

d. Activity

The effect of a ganglion blocking drug increases as the activity of the ganglion exposed to it increases or is prolonged. For instance, in the cat, hexamethonium depresses transmission through the superior cervical ganglion more when the rate of stimulation of the preganglionic trunk is at 30 shocks/sec. than when at 10 shocks/sec. With doses of hexamethonium that only partially paralyze the ganglion, transmission may be good when continuous excitation is first started, but soon begins to fail, rapidly at first, and then more slowly as excitation is maintained. In man, some subjects have reported that, after administration of hexamethonium, ocular accommodation may be normal for a few moments and then it flags, so that only very brief periods of reading are possible; similarly the pupillary reaction to light may start briskly and then wane as the stimulus is maintained. These observations may be regarded as reflecting an increased " fatigability " of ganglionic transmission when the ganglion is partially blocked. The fact that the over-active ganglion is the most sensitive possibly confers some selectivity of action.

e. Maximality

Evidence has been brought that complete ganglionic block can sometimes not be obtained with tetraethyl ammonium. Certain facts suggest that this may sometimes be the case with hexamethonium; for instance, the blood pressure of a cat given hexamethonium is never as low as that of the pithed animal. On the other hand, in man hexamethonium is capable of producing an increase in the blood flow in the leg comparable with that following block of the lumbar sympathetic nerves (Schnaper *et al.* 1951). Moreover, even resistant ganglion cells, such as those supplying the nictitating membrane in the cat, can be completely paralyzed if sufficient dosage is given. In clinical use, therefore, it is probable that some ganglia will be completely paralyzed fairly readily but others may not be fully blocked by doses that can be given in practice. Unfortunately there is no way of predicting which ganglia will be fully sensitive and which relatively resistant.

2. Cardiovascular Effects of Hexamethonium in the Normal Subject

In the normal individual the injection of 20–50 mg. of hexamethonium has little effect so long as the subject is supine. There may be a small fall in systolic and diastolic blood pressure but often there is no significant change. Similarly the pulse rate is not much altered, although there may be slight acceleration. The extremities and face become slightly flushed and warmer, particularly if the subject is in cool surroundings. The conjunctivae become injected and the subject looks as though he had just woken up. At the same time there is a rather variable effect on the eyes. In some subjects there is dilation of the pupil, weakening of the reaction to light and paralysis of accommodation—effects which may lead to difficulty in reading and to complaints of glare in bright light: others may be almost free of these effects. (See Arnold, Goetz & Rosenheim, 1949; Arnold & Rosenheim, 1949; Burt & Graham, 1950; Finnerty & Freis, 1950; Grob & Harvey, 1950.)

a. Postural Hypotension

On standing, postural hypotension usually develops. Its extent depends both on the duration of standing and on the individual. In some subjects, although there may be a further fall in blood pressure on standing, this does not progress to levels sufficiently low to produce faintness. In others, the fall in blood pressure may be progressive and lead to transient loss of consciousness sometimes accompanied by a more or less typical vaso-vagal attack. The liability to postural hypotension outlasts considerably any effect on the supine blood pressure. Postural hypotension produced by hexamethonium is of great importance in its use, sometimes being deliberately exploited to produce a desired fall in blood pressure, sometimes being the cause of unexpected collapse. At least two factors may contribute to it: depression of the reflex vasoconstriction, which normally takes place when the patient stands up, to maintain cerebral blood flow, and pooling of blood in the legs and viscera. The importance of the latter is demonstrated by the prompt relief which may be obtained by walking or by contracting the abdominal muscles.

The cause of the variation in the effects of hexamethonium has been analyzed in some detail (Morrison & Paton, unpublished). Some of it can be attributed to differences in absorption from the intestine or even from the site of subcutaneous injection. It may also in part be due to differences in the volume of fluid through which the drug is distributed in the body, and to differences in excretion caused by variations in glomerular filtration rate. But even when these factors are allowed for, important differences in sensitivity remain. If estimates of the concentration of hexamethonium in the plasma are related to the reduction of the systolic blood pressure after standing for a given test period, an index of sensitivity may be obtained, expressed as the percentage fall in blood pressure per microgram of hexamethonium in the plasma. Such an index has so far been found to range from 3 to 25. The cause of this eightfold variation in response to comparable plasma concentrations of hexamethonium is unknown, and contrasts sharply with the quite regular effect of hexamethonium when tested under standardized conditions in an experimental animal. There are several possible explanations; the postural reactions are relatively complex and depend on the vigour of vasomotor reflexes, on the vascular capacity of the lower limbs and splanchnic area, and probably also on muscle tone. There is a fairly general impression, not yet properly analyzed, that old subjects, particularly those with arteriosclerosis, are liable to larger falls in blood pressure than young subjects with healthy blood vessels.

b. Effects on Other Vascular Reflexes

Effects on other vascular reflexes have been described in addition to the depression of postural adjustments already

mentioned (Finnerty & Freis, 1950; Freis *et al.* 1951). If blood is trapped in the lower limbs by the application of a cuff to the thigh, inflated to 60–80 mm. Hg, a much bigger fall in blood pressure occurs after hexamethonium than in normal subjects, and this fall may be sufficient to cause faintness and collapse. The amount of blood trapped in the limb does not appear to be different under the two conditions, although the rate at which the volume of blood in the limb increases is faster after administration of hexamethonium. Similar results are obtained following haemorrhage (Enderby *et al.* 1951; Freis *et al.* 1951); in the normal individual as much as 500 ml. may be removed with usually only trivial effect on the blood pressure. After hexamethonium, however, the removal of only 100 ml. (between 2% and 3% of the blood volume) may produce a substantial fall in blood pressure, which continues as more blood is removed. When the blood is restored to the circulation the blood pressure returns again quite precisely to its original level.

It seems clear from these observations that the response of the body to procedures which diminish the circulating blood volume involves a vigorous autonomic component, and that this is very sensitive to hexamethonium. It may well be that postural hypotension, in its severer forms at least, is in part a " physiological exsanguination " of the same type, in which blood pooled in peripheral vascular reservoirs is effectively removed from the circulating blood volume.

Interesting studies are suggested by these observations, for if the compensatory reactions to haemorrhage can be eliminated, it should be possible to study more readily some of the hydrodynamic characteristics of the vascular bed. It would be interesting to know, for instance, whether after hexamethonium the arteriosclerotic subject is more sensitive to haemorrhage than the subject with healthy vessels; if so, one might be able to develop a physiological criterion of hardening of the arteries, in terms of the reduction of blood volume which, after administration of hexamethonium, will lower the blood pressure by a given amount.

Hexamethonium also abolishes the pressor reflexes which follow the Valsalva manoeuvre, exposure of the hand to cold and the return from tilting (Finnerty & Freis, 1950).

c. " *Controlled Circulation* "

It had previously been shown that bleeding at operation can be diminished in two ways: either by withdrawing blood from the patient or by the induction of spinal anaesthesia. Both these procedures cause a substantial lowering of blood pressure. Ganglion blocking agents have been used for the same purpose and we owe the development of this hypotensive technique in surgery chiefly to Enderby and his colleagues (Enderby, 1950; Enderby & Pelmore, 1951; Enderby *et al.* 1951; Hughes, 1951; Lewis, 1951; Shackleton, 1951). It has been found that doses of hexamethonium of between 20 and 50 mg. injected intravenously, combined with postural assistance, will reduce the blood pressure to levels of the order of 60 mm. Hg. When this has been achieved, remarkably dry operative fields may be obtained under a wide variety of surgical conditions. Particularly satisfactory results have been recorded in ear, nose and throat operations, in plastic surgery, and in thyroidectomy and mastectomy; but the method has been successfully used in general surgery of all kinds. A recent development has been in neurosurgery (Guiot, Damoiseau & Poloukhine, 1951; Vourc'h, 1952). Here the hypotensive technique has been used, not only to diminish bleeding but also to reduce intradural pressure and cerebral oedema and to improve the visibility of the operative field.

Apart from the relevance of this work to anaesthesia it has many points of general interest and provides a good deal of information about the circulation in normal individuals under the influence of hexamethonium. In the first place it is remarkable that the hypotension obtained may be prolonged for hours without harm to the patient, although the levels of blood pressure are such as would commonly be regarded (and, indeed, were at first regarded) as those of profound circulatory " shock ". A similar hypotension induced by haemorrhage, for instance, is known to enter an irreversible stage which is not overcome even by the restoral of the blood volume. There must be, therefore, a fundamental difference between the hypotension obtained by the removal of vasoconstrictor tone combined with posture, and the hypotension which follows haemorrhage. It was early pointed out that in the former case vasoconstrictor tone is removed, whereas in the latter it will be intensified. Hence under the influence of hexamethonium the capillary blood pressure and flow may well be within normal limits, in spite of the low arterial blood pressure, whereas after haemorrhage there must be a much diminished capillary circulation. Similarly, the hypotension following ganglionic paralysis and postural adjustment is in sharp contrast with that produced by histamine, which—like haemorrhage—causes a prolonged circulatory failure outlasting the causal agent, due (in the case of histamine) to a widespread and unphysiological capillary dilatation and to damage to capillary permeability. The hypotension with hexamethonium resembles most closely that produced by infusion of acetylcholine. Dale & Laidlaw (1919) compared in detail the differences between histamine shock and the effects of acetylcholine, and commented explicitly on the rapid return of the blood pressure to normal when the acetylcholine infusion was stopped. Important elements in the safety of the hypotension after hexamethonium administration can thus be recognized as the absence of peripheral vasoconstrictor tone, and the presence of normal dilatation and permeability in the capillary bed.

The evidence that blood flow to vital organs is in fact adequate during this degree of hypotension is not complete. The flow through the coronary arteries is difficult to measure directly in man. In animals massive doses of hexamethonium are known to have trivial effect on the coronary blood flow (Wien & Mason, 1951). In many cases the only information so far gleaned is that no electrocardiographic changes have been observed, even in arteriosclerotic subjects exposed to the hypotensive technique (Enderby *et al.* 1951). In one or two subjects liable to angina, who have been treated for hypertension with hexamethonium, anginal attacks have been precipitated when too great a fall in blood pressure was produced, but the symptoms subsided when the blood pressure was restored by the patient's lying down.

The circulation through the kidneys during hexamethonium hypotension has been studied in anaesthetized patients (Miles *et al.* 1952). It was found that, under conditions of light anaesthesia when the renal blood flow could be still further depressed by deepening the anaesthesia, hexamethonium in doses sufficient to produce the usual hypotension did not reduce the renal blood flow. It has also been found in normal subjects that the rate of excretion of hexamethonium, which is cleared in the same way as inulin

corresponds fairly well to clearance at the normal glomerular filtration rates; so that, with ordinary doses in normal subjects, the glomerular filtration rate during the action of hexamethonium remains within normal limits (Morrison & Paton, unpublished).

The circulation through the brain has not been studied in detail, but the use of the hypotensive technique in neurosurgery has shown that, with careful continuous control of posture, a low blood pressure may be maintained without limiting the consciousness or co-operativeness of the patient, and without causing alteration in electroencephalograms recorded from the cortex (Guiot *et al.* 1951; Vourc'h, 1952).

Measurements of the cardiac output are still lacking. Werkö *et al.* (1951) found that in hypertensives the cardiac output sometimes fell and sometimes did not. The results on renal blood flow (Miles *et al.* 1952) imply that the cardiac output cannot be greatly reduced, otherwise the renal blood flow would have represented an improbably large fraction of the total cardiac output. The general picture, therefore, of the circulation in the subject under the influence of hexamethonium, with careful postural adjustments sufficient to bring the blood pressure down to about 60 mm. Hg, is of a cardiac output that may not be far from normal, furnishing a blood supply adequate for the most important organs.

The second problem arising is that of how the reduction in bleeding is brought about. An antihaemorrhagic effect of the kind observed could be due (i) to a reduction of blood flow, (ii) to a reduction of the hydrostatic pressure within the cut vessels, (iii) to a change in the path of the blood within a tissue, so that it traverses vessels from which bleeding occurs less readily, or (iv) to some enhancement of the clotting mechanism itself. Of these possibilities the fourth can probably be excluded, since there is no evidence that hexamethonium can affect coagulation in vitro or in vivo and since it is not a compound of the type likely to be involved in such reactions. The other three mechanisms may all play their part, although the relative importance of each is still uncertain. The fact that blood pressure is so low will certainly mean that the pressure in arteries and arterioles against which a clot has to form and maintain itself is correspondingly reduced. But to this may well be added the effects of a reduction in tissue blood flow from two causes: (i) the tissue concerned may be raised above the rest of the body, and with the prevailing low arterial pressures (provided the veins are collapsible) even fairly small elevations may reduce considerably the blood flow to the part concerned; (ii) the use of posture to pool blood in the dependent parts may on some occasions reduce the cardiac output. If such a reduction in blood flow occurs in the tissues of the operative field, then the term "postural ischaemia" would be merited; but there is no decisive evidence yet that the tissues are in fact ischaemic, for pallor is not a reliable sign, and the reduction of bleeding may be due to other causes.

The third possibility is raised by recent work on the intimate organization of the vascular system, which has brought to light a system of vascular shunts in parallel with the capillary bed. It may well be that when vasoconstrictor tone is removed, blood passes along a rather different path from artery to collecting vein than when normal tone is present, and that the ease of clotting and the firmness of the clot differ with the alternative paths.

The success of this hypotensive technique corresponds in many ways to the success of the use of muscle relaxants in anaesthesia. The use of ganglion blocking agents means that "controlled circulation" is now possible just as "controlled respiration" is already well recognized. The dangers of both techniques are also comparable and the patient in whom natural circulation has been suspended is as vulnerable as the subject incapable of spontaneous respiration. The main danger is that of being placed in a dangerous posture, but other difficulties may occur; for instance, the low blood pressure may mean that pressure on the body at weight-bearing points more readily produces ischaemia of the skin and bed-sores.

Hexamethonium has also been employed to stop haemorrhage occurring accidentally during operation; for instance, bleeding from a gastric artery and from a pulmonary vein were promptly and permanently checked (Harper, 1951; Rollason, 1951). Its use in this way is dangerous of course because the effects of haemorrhage are increased in the presence of ganglionic blockade so that, if bleeding has been serious, hexamethonium may produce too great a fall in blood pressure.

3. Hexamethonium in the Treatment of Hypertension

The recognition of the existence of nervous factors in the genesis of hypertension paved the way for therapy by interference with abnormal vasomotor autonomic activity, particularly by means of ganglionic blockade. But it must be remembered that, so long as the still vigorous debate about the cause of hypertension continues, therapy is fundamentally empirical.[1]

In practice, hexamethonium usually relieves symptoms and lessens signs of hypertension, especially in severer cases entering on the malignant phase (Campbell & Robertson, 1950; Campbell, Graham & Maxwell, 1952; Finnerty & Freis, 1950, 1951; Kilpatrick & Smirk, 1952; Mackey & Shaw, 1951; Murphy, 1951; Restall & Smirk, 1950, 1951; Rosenheim, 1952; Savile, 1950; Smirk & Alstad, 1951; Turner, 1951), although disappointing results have occurred in some cases (Locket, Swann & Grieve, 1951; Locket *et al.* 1952). Headache, breathlessness and dizziness are normally lessened or removed. Pulmonary oedema may be relieved, and cerebral oedema and vomiting arrested. Enlargement of the heart may regress. Papilloedema diminishes, and retinal damage, if it has occurred, may be repaired. Similar results are reported in the few cases of toxaemia of pregnancy and of eclampsia where hexamethonium has been used, permitting a live birth or terminating status eclampticus (Penny & Shackleton, 1951; Turner, 1951). Hexamethonium passes the placental barrier fairly readily (Young, 1952), but no ill-effects on the foetus have been described.

There are two important practical features in the treatment of hypertension. The first is that there is considerable variation in the response of patients, just as there is in the response of normal subjects. This variation corresponds, to some extent, with the degree of the neurogenic element in the hypertension; thus the fall in blood pressure obtained by a given test dose of hexamethonium matches roughly the fall in blood pressure that can be achieved by sedation (Arnold *et al.* 1949). It is extremely difficult, however, to predict what dose is going to be required, and for practical purposes it is safest to start with a fairly small test dose, e.g. 25 mg. subcutaneously.

[1] See articles elsewhere in this Bulletin by Pickering (p. 305) and Wilson (p. 316).

A fall in blood pressure can be obtained in almost every case if postural measures are also used, so that, even where the neurogenic element is slight, some reduction in blood pressure is possible.

The second practical point in treatment, which is also of theoretical interest, is the development of tolerance to hexamethonium. As treatment proceeds, a dose of hexamethonium which was previously effective gradually loses its action and has to be considerably increased in order to produce its original effect. This process seems to continue over a period of a few weeks, at the end of which time the dose may have increased as much as tenfold. The increased tolerance is lost fairly rapidly when treatment is suspended. It is uncertain whether the tolerance is restricted to the effect on the blood pressure or not; it may be that the other ganglionic systems also acquire some resistance to hexamethonium, but if so it is certainly less well developed than in the cardiovascular system; for instance, constipation or paralysis of accommodation may become increasingly severe as a patient develops tolerance and has to be given larger doses. This accommodation by the organism to the hypotensive effects of hexamethonium may be compared on the one hand to the recovery of vascular tone after sympathectomy or, on the other, to restoration of the original hypertension by humoral compensatory mechanisms. The phenomenon deserves much closer investigation.

The unreliability of oral absorption, the variation among individuals, and the development of tolerance, have made it necessary to develop a special method of administration, and the " insulin regime " described by Smirk has proved most satisfactory thus far. Papers by Smirk & Alstad (1951), Turner (1951), Freis (1951), and Rosenheim (1952) should be consulted for details of the induction and maintenance of treatment.

As a rule it seems necessary for treatment with hexamethonium to be continued more or less indefinitely. Some cases have been reported in which the benefits of treatment outlasted the treatment itself, and it was hoped that it might prove possible by a period of intensive therapy to break the hypertensive " vicious circle ", but the occurrence of occasional natural remissions in the disease means that there is no real evidence of this so far.

a. Comparison of Hexamethonium with Other Drugs

Tetraethylammonium was the first ganglion blocking agent used in hypertension and proved a useful and stimulating research tool, with which interest in the approach to therapy of hypertension through autonomic ganglia was awakened. Its transience, side-actions (paraesthesia, occasional " curariform " action, and so on) and ability to provoke adrenaline secretion, have limited its clinical usefulness.

Other ganglion blocking agents include tetra- and pentamethonium, the dimethylethyl analogue of hexamethonium (M. & B. 1863) ($N(CH_3)_2C_2H_5.(CH_2)_6N^+(CH_3)_2C_2H_5$) (Locket *et al.* 1951) and Pendiomide, an analogue of pentamethonium: these have been less closely studied, but seem to have properties indistinguishable in man from those of hexamethonium save for being, respectively, much less, slightly less, slightly more and slightly less active (Barnett, 1951; Burt & Graham, 1950; Enderby, 1950; Enderby & Pelmore, 1951; Kay & Smith, 1951; Wien & Mason, 1951).

A variety of other agents has received attention in recent years, particularly thiocyanate, sympatholytic agents, nitrites and the veratrum alkaloids. All of these have proved capable of producing a fairly sustained fall in blood pressure in normal and hypertensive subjects. But in each case the use of the drug is complicated by additional and diverse toxic effects which restrict treatment more or less severely. Hexamethonium provides an interesting contrast; the difficulties in its use do not spring from any additional toxic action of this kind, from which it is remarkably free, but principally from the danger of too intense an action of the kind used therapeutically, leading to too great a fall in blood pressure in an organism accommodated to the hypertensive state, or to the paralysis of other ganglia (including those concerned with ocular accommodation and with intestinal function). With the former drugs, a balance has to be struck between the therapeutic action and undesired action of quite a different sort. With hexamethonium, virtually all its effects are due to ganglionic blockade, and the problem is to adjust the intensity of this. Could this be done satisfactorily, the most serious difficulty of treatment would be removed.

It need not be assumed that only one of these drugs should be used at one time. Patients on a low sodium diet are known to be more sensitive to hexamethonium. It may be, therefore, that a combination or alternation of hexamethonium with such a diet, or with one of the other drugs mentioned, or with less well-known compounds, may provide an effective and more easily controlled regime.

4. Other Peripheral Vascular Effects of Hexamethonium

Hexamethonium has been used for other conditions affecting the cardiovascular system (Arnold *et al.* 1949; Burt & Graham, 1950; Finnerty & Freis, 1951). It has been as successful as paravertebral sympathetic block in increasing the blood flow to the lower limb in cases of occlusive arterial disease.[2] Raynaud's phenomenon can be checked by hexamethonium. It has been used successfully in the treatment of causalgia (Rose & Wemple, 1951). Its use in these fields is limited by the fact that a general ganglionic paralysis is obtained where an action restricted to a particular limb or limbs is required. The reason for the effectiveness of hexamethonium in causalgia is obscure. It has itself no general or local anaesthetic activity and it acts presumably by increasing the blood flow either to the damaged nerve or to the adjacent tissues.

It would be interesting to know more clearly the effects of hexamethonium in two other situations: the pulmonary vessels and the cerebral vessels. Evidence has accumulated that there is an effective vasomotor control of the pulmonary vessels and that tetraethylammonium can sometimes diminish the pulmonary vascular resistance. Certain anaesthetists have commented on the ease with which a patient may be kept oxygenated when hexamethonium is being used to diminish bleeding, and it seems possible that pulmonary vasodilatation by hexamethonium can contribute to this. There is also evidence that the cerebral vessels are under effective vasomotor control and this is of interest in the pathogenesis of migraine. The therapeutics of this condition are distinctly confused, since ergotamine, first introduced as a sympatholytic, is now believed to act not by relieving sympathetic vasospasm but by causing vasoconstriction; and further, dihydroergotamine appears to be equally effective in treatment

[2] See articles elsewhere in this Bulletin by Learmonth & Slessor (p. 375) and Goodwin (p. 371).

but is much less effective as a vasoconstrictor. It would be useful to know whether interruption of autonomic activity with hexamethonium would relieve or accentuate the migrainous attack.

5. Conclusion

Ganglion blocking agents are pharmacologically a somewhat novel type of drug in therapeutics, and the techniques of handling them are still being evolved. It is highly probable that hexamethonium will be replaced by more satisfactory agents, although none offering any substantial advantage has yet appeared; but the lessons learned with hexamethonium should be applicable without serious modification to the use of other drugs acting in the same way. In the meantime its purity of action, restricted to a remarkable degree to autonomic ganglia, makes the technique of ganglionic block with hexamethonium worth careful study, and one the results of which provide fairly clear-cut information.

Finally it may be noticed that with the aid of ganglion blocking drugs many stimulating observations in human physiology and pathology have been made, such as the fact that a low blood pressure can be safely maintained without producing " shock ", and that in the hypertensive patient tolerance to hexamethonium develops. It may be in these observations, as much as in any immediate clinical usefulness, that the importance of ganglion blocking agents will ultimately be found to lie.

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